UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/732,783	12/10/2003	David M. Hone	4115-122 DIV 2	6909

23448 7590 04/18/2006

INTELLECTUAL PROPERTY / TECHNOLOGY LAW
PO BOX 14329
RESEARCH TRIANGLE PARK, NC 27709

EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 04/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/732,783	HONE ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *162* is/are pending in the application.

4a) Of the above claim(s) *8-60 and 62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 61* is/are rejected.

7)☒ Claim(s) *1-7 and 61* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/18/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Office Action

Status of the Claims

Applicants' election of Group I (claims 1-7 and 61) in the communication received 01 February, 2006, is acknowledged. Because applicant did not distinctly and specifically point out the purported errors in the restriction requirement, the election has been treated as an election without traverse (refer to M.P.E.P. § 818.03(a)). Claims 8-60 and 62 are withdrawn from further consideration by the examiner, pursuant to 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

35 U.S.C. § 120

Applicants are reminded of the requirements pursuant to 35 U.S.C. § 120. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. The first paragraph of the specification should be amended to reflect the developments in U.S. Serial No.: 09/383,709 (now U.S. Patent No.: 6,841,345).

37 C.F.R. § 1.98

The information disclosure statement filed 18 March, 2004, has been placed in the application file and the information referred to therein has been considered.

Claim Objections

Claims 1-7 and 61 are objected to because they fail to reflect the restriction/election requirement. Applicants are required to amend the claim language to reflect the election (i.e., A method of treating or preventing immunodeficiency virus infection through the administration of a lipopolysaccharide **variant**, wherein said

variant...).

35 U.S.C. § 112, Second Paragraph

Claims 1-7 and 61 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The reference to "substantially no pyrogenicity or reduced pyrogenicity relative to lipopolysaccharide" is vague and indefinite. First, it is not clear what constitutes a substantial reduction in pyrogenicity. For instance, would a reduction of 10% be substantial? What about a 20% or 50% or 90% reduction? Second, the reference to any lipopolysaccharide is ambiguous. Applicants should clearly identify the reference molecule (i.e., wherein the pyrogenicity of the LPS variant is 20-fold less as compared to the wildtype E. *coli* parent LPS molecule). The reference to induced secretion of various β-chemokines is also vague and indefinite. It is not readily manifest to the skilled artisan as to which cytokines are affected by the claimed compound. Applicants should amend the claim language, as supported by the disclosure, to clearly set forth the salient characteristics and properties of the LPS variant (i.e., wherein said LPS variant displays a 20-fold reduction in pyrogenicity as compared to wildtype and induces the secretion of MIP-1α).

Claims 1 and 2 are also confusing in their reference to an "immunodeficiency virus infection" in a human subject and an HIV infection in a human subject. To date, the Examiner is only aware of two viruses that cause immunodeficiency virus infections in humans and these viruses have been termed human immunodeficiency virus types 1 and 2 (HIV-1 and -2). Since the claims are directed toward human immunodeficiency virus infections, it would seem that

the claims already encompass HIV-1 and -2 infections. Applicants should amend the claim language, as supported by the disclosure, to clearly identify the virus(es) of interest (i.e., A method of preventing human immunodeficiency virus infection [claim 1]; ... wherein said human immunodeficiency virus is HIV-1 [claim 2]).

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 1-7 and 61 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *Univ. of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 920, 69 U.S.P.Q.2d 1886, (Fed. Cir. 2004). *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 U.S.P.Q.2d 1609, (Fed. Cir. 2002). *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 U.S.P.Q.2d 1398, (Fed. Cir. 1997). *Fiers v. Revel Co.*, 984 F.2d 1164, 25 U.S.P.Q.2d 1601, (Fed. Cir. 1993). *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 U.S.P.Q.2d 1016, (Fed. Cir. 1991). *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981). *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976).

To satisfy the written description requirement, a patent

specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Vas-Cath, Inc., v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116. The issue raised in this application is whether the original application provides adequate support for the broadly claimed genus of lipopolysaccharide variants. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997). The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the biomolecule of interest. *In re Bell*, 991 F.2d 781, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1993). *In re Deuel*, 51 F.3d 1552, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995). A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 U.S.P.Q.2d 1895, 1905 (Fed. Cir. 1995). The court noted in this decision that a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a

genus because it would not reasonably lead those skilled in the art to any particular species.

An applicant may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. For some biomolecules, examples of identifying characteristics include a nucleotide or amino acid sequence, chemical structure, binding affinity, binding specificity, and molecular weight. The written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. Without such a correlation, the capability to recognize or understand the structure form the mere recitation of function and minimal structure is highly unlikely. In the latter case, disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement. *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566, 43 U.S.P.Q.2d 1398, 1404, 1406 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998). *In re Wilder*, 736 F.2d 1516, 1521, 222 U.S.P.Q. 369, 372-3 (Fed. Cir. 1984). Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a

known or disclosed correlation between structure and function, and the method of making the claimed invention.

The claims of the instant application are broadly directed toward a method of treating or preventing any immunodeficiency virus infection by administering a lipopolysaccharide variant. Thus the claims encompass the administration of a broad class of chemical compounds with disparate structures and activities. The disclosure describes the isolation and purification of a single non-pyrogenic LPS variant that was obtained from the *Escherichia coli htrB*1::Tn10, *msbB*::Ω*cam* double mutant MLK986. However, the specification fails to disclose the isolation and purification of LPS variants from any other microorganisms with the desired properties. Moreover, the LPS molecule is large and complex. The disclosure fails to teach which chemical modifications lead to the desired properties. Accordingly, the skilled artisan cannot readily envisage any particular LPS variant. Therefore, the skilled artisan would reasonably conclude that applicants were not in possession of the claimed invention at the time of filing. Appropriate amendment of the claim language to reflect the single disclosed non-pyrogenic LPS variant would be acceptable.

Enablement

Claims 1-7 and 61 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are broadly directed toward methods for the treatment or prevention of immunodeficiency virus infections in humans through the administration of a lipopolysaccharide variant with reduced pyrogenicity and an ability to induce β-chemokine expression.

The legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:
1) The disclosure fails to identify those critical molecular determinants that modulate the pyrogenicity and immunological properties of any given LPS variant or mutant. For instance, the disclosure fails to teach which portions of the LPS outer core or backbone are responsible for the pyrogenic and immunological properties of the molecule. The disclosure also fails to provide any guidance pertaining to those sugar residues that need to be retained or those that can be deleted or altered.
2) The disclosure fails to provide adequate guidance pertaining to the preparation of suitable LPS variants. The disclosure describes the preparation of LPS from a single *Escherichia coli* double mutant designated strain MLK986 (this strain is an W3110 *htr*B1::Tn10, *msb*B::Ωcam double mutant). A detailed characterization of the mutant strain (i.e., location of the mutation within any given gene) and LPS derived therefrom was not provided. The disclosure fails to identify the modifications that have taken place in the LPS molecule that lead to the altered properties. The disclosure also fails to assess the stability of said mutant and its effect on

LPS expression. For instance, is the mutated gene completely inactive or does it produce an enzymatic product with reduced activity?

3) The prior art teaches that the generation of stable bacterial mutants through transpositional mutagenesis is often problematic and often results in the production of leaky or unstable mutants (Cornelis *et al.*, 1992; Pries *et al.*, 1992). Transpositional mutagenesis is a random process that provides the investigator with little or no control over the insertion process. The transposon may integrate adjacent to the gene of interest or directly in the gene of interest. Such actions may result in complete abrogation of enzyme activity, the production of enzymes with different activities, or the production of an enzyme that essentially displays wildtype activity. All of these mutants may lead to the production of different LPS preparations with differing structures and activities.

4) The disclosure fails to provide any working embodiments. As noted *supra*, the disclosure teaches the isolation and preparation of LPS from a single E. *coli* double-mutant designated strain MLK986(*htr*B1::Tn10, *msb*B::Ωcam double mutant). Experiments performed in an *in vitro* tissue culture system demonstrated that pretreatment of HIV-1_{BAL}-infected PBMC-derived monocytes with this LPS resulted in the inhibition of HIV-1 viral replication. However, this example does not constitute a proper working embodiment because such simple *in vitro* tissue culture systems are not generally predictive of clinical efficacy.

5) The prior art teaches that the development of antivirals for the treatment of HIV-1 infection has met with limited success (Öberg and Vrang, 1990; Yarchoan and Broder, 1992; Gait and Karn, 1995; Flexner and Hendrix, 1997). Several factors have contributed to this general failure such as the lack of correlation between *in*

vitro and *in vivo* models and the clinical setting. Many models fail to accurately assess the pharmacological profiles of potential therapeutics. They also fail to take into consideration the high viral burden associated with HIV-1 infection (upwards of 10^{10} viral particles are produced per day), the sequestration of virus in the lymphatic system and central nervous system, and the ability of the virus to exist in a latent state. Moreover, the quasispecies nature of HIV-1 infection often leads to clinical failure because of the rapid development of antiviral resistance.

6) The prior art, in contrast to applicants' findings, also appears to suggest that the addition of LPS may actually result in the activation of HIV-1 replication in monocyte/macrophage-like cell lines. Pomerantz and colleagues (1990) reported (see p. 253, Summary) that "Lipopolysaccharide (LPS) potently stimulates human immunodeficiency virus type 1-long terminal repeat (HIV-1-LTR) CAT constructs transfected into monocyte/macrophage-like cell lines ... LPS is also shown to dramatically increase HIV-1 production from a chronically infected monocyte/macrophage-like cloned cell line, U1, which produces very low levels of HIV-1 at baseline." Moriuchi and associates (2000) recently reported (see p. 2041, Abstract) that "supernatants from macrophages exposed to the bacterial product lipopolysaccharide can induce *in vitro* activation of HIV-1 from latently infected, resting $CD4^+$ T cells obtained from HIV-infected individuals." Thus, the skilled artisan would be reluctant to employ LPS variants as a therapeutic for the treatment or prevention of HIV-1 infection at this point in time.

7) The claims are of considerable breadth and encompass LPS variants obtained from any source. The claims further include a list of sundry gram negative bacteria and attendant target genes that can be mutated and LPS prepared from. However, as set forth *supra*, the disclosure is defective and fails to support such

breadth. Moreover, many of the genes responsible for LPS metabolism in different bacteria display considerable genetic diversity (i.e., the *htr*B gene of *Haemophilus inluenzae* and E. *coli* only share 56% genetic relatedness at the amino acid sequence level) thereby making direct extrapolations between different bacterial systems questionable.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, James C. Housel, can be reached at (571) 272-0902. Direct general status inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Applicants are reminded that the United States Patent and Trademark Office (Office) requires most patent related correspondence to be: **a)** faxed to the Central FAX number (571-273-8300) (updated as of July 15, 2005), **b)** hand carried or delivered to the Customer Service Window (now located at the Randolph Building, 401 Dulany Street, Alexandria, VA 22314), **c)** mailed to the mailing address set forth in 37 C.F.R. § 1.1 (e.g., P.O. Box 1450, Alexandria, VA 22313-1450), or **d)** transmitted to the Office using the Office's Electronic Filing System. This notice replaces all prior Office notices specifying a specific fax number or hand carry address for certain patent related correspondence. For further information refer to the Updated Notice of Centralized Delivery and Facsimile Transmission Policy for Patent Related Correspondence, and Exceptions Thereto, 1292 Off. Gaz. Pat. Office 186 (March 29, 2005).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access

to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

Jeffrey S. Parkin, Ph.D.
Primary Examiner
Art Unit 1648

15 April, 2006